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RESEARCH PAPER

Evaluation of orally disintegrating films containing ferulic acid inclusion complexes: Physical characteristics and release kinetics

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Abstract

Orally disintegrating films (ODFs) has gained significant attention as a nutrient delivery platform due to its ease of intake. But studies on delivering ferulic acid (FA) through ODFs are still scarce. The objective of this study was to assess the physical characteristics of ODFs containing FA/β-cyclodextrin (0.5:1) (FA/β-CD (0.5:1)) and FA/hydroxypropyl-β-cyclodextrin (0.5:1) (FA/HP-β-CD (0.5:1)) complexes, as well as analyze the release kinetics of FA in both ODFs. Confirmation of the FA/β-CD (0.5:1) and FA/HP-β-CD (0.5:1) inclusion complexes was achieved through the reduction or attenuation of FA's distinctive peaks in FT-IR and XRD examinations. Both the ODFs containing FA/β-CD (0.5:1) and FA/HP-β-CD (0.5:1) had a thickness of 0.06 mm, a surface pH of 6.7, and a disintegration time of less than 30 s, all of which met the requirements of ODFs effectively. The release of FA in both ODF formulations exhibited a high degree of consistency with the first-order kinetic model. Furthermore, the FA/HP-β-CD (0.5:1) ODF exhibited a higher cumulative release rate compared to the FA/β-CD (0.5:1) ODF throughout the entire *in-vitro* digestion process, indicating that FA/HP-β-CD (0.5:1) was more suitable for ODF formulation.

Keywords

β-Cyclodextrin, Ferulic acid, Hydroxypropyl-β-cyclodextrin, Orally disintegrating films, Physical characteristics, Release profiles

Introduction

The global demographic trend indicates a significant increase in the population aged 60 and above, with certain nations experiencing pronounced aging challenges. Enhancing the nutritional status of the elderly is crucial for sustaining their health. Ferulic acid (FA), a secondary metabolite prevalent in fruits (Giuffrè et al. 2017), vegetables (Samiaa 2023) and cereals (Palaniswamy and Govindaswamy 2017; Hu 2025), is recognized for its extensive biological functions, including the treatment of Alzheimer's disease and the prevention of cardiovascular disorders (Chowdhury et al. 2019). Nevertheless, the industrial application of FA is hindered by its limited water solubility (Sohn and Oh 2003). Consequently, the development of delivery systems is regarded as an effective strategy to preserve its health-promoting properties.

Various encapsulation and delivery systems, such as microemulsions (Lu 2016), liposomes (Ara et al. 2023), and hydrogels (Wang et al. 2020), have been devised to improve the solubility of FA. Previous research has predominantly concentrated on delivery systems that facilitate nutrient absorption through the gastrointestinal tract. However, it is crucial to recognize that oral mucosal absorption constitutes another significant pathway following ingestion.

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In recent years, orally disintegrating films (ODFs) have attracted considerable attention as an innovative delivery system for pharmaceuticals and nutritional supplements. This interest is largely due to the rapid disintegration of the ODFs upon contact with saliva, which facilitates the swift absorption of active ingredients through the oral mucosa. This mechanism bypasses first-pass hepatic metabolism, thereby enhancing bioavailability (Pacheco et al. 2021), and offering more efficient absorption compared to the gastrointestinal tract(Yuan et al. 2022). Additionally, ODFs are advantageous due to their portability and the elimination of the need for water during administration, providing convenience for children and individuals experiencing emesis who require immediate nutritional supplementation. ODFs are also particularly advantageous for elderly individuals who face difficulties with swallowing or chewing. Therefore, ODFs may hold the potential as a promising method for delivering active ingredients to the elderly population within the medical and food industries.

There has been an increasing interest in investigating ODFs as a promising medium for the delivery of active ingredients, including probiotics (Heinemann et al. 2013), vitamins, (Kose et al. 2022) melatonin (Musazz et al. 2019), proteins (Borges et al. 2016), and functional extracts (Kose et al. 2022). This interest is largely attributed to the patient compliance and convenience associated with ODFs (Garcia et al. 2020). Nonetheless, research on the delivery of FA via ODFs remains limited. The direct incorporation of FA into ODFs may adversely affect their disintegration and mechanical properties. The formation of an inclusion complex with cyclodextrin has been proposed as a viable strategy to address this issue. Both β-Cyclodextrin (β-CD) and hydroxypropyl-β-cyclodextrin (HP-β-CD) exhibit a distinctive amphipathic nature, facilitating the formation of host-guest complexes through encapsulation (Wankar et al. 2020). This property makes them promising candidates for enhancing the solubility of active ingredients (Aldawsari and Badr-Eldin 2020). In a study conducted by Sha et al. (2022a), it was demonstrated that the incorporation of less than 10% (w/w) β-CD led to the uniform dispersion of pre-gelatinized cassava starch and the development of a more complete network structure in the production of ODFs. Our previous research had optimized the formulation of ODF containing FA/β-CD (0.5:1) and FA/HP-β-CD (0.5:1) complexes. However, the physicochemical properties and release kinetics of ODFs containing FA/β-CD (0.5:1) and FA/HP-β-CD (0.5:1) have been scarcely compared till now.

The objective of this study was to investigate the physicochemical properties of hydroxypropyl methylcellulose (HPMC) based ODFs containing FA/β-CD (0.5:1) and FA/HP-β-CD (0.5:1) inclusion complexes. Additionally, the release properties of FA from both films were evaluated using simulated oral, stomach, and intestinal models. The findings of this research may contribute to the advancement of functional ODFs that facilitate the oral delivery of active ingredients.

Materials and methods

Materials

FA (99% purity), HP-β-CD (≥98.0%), and β-CD (≥98.0%) were purchased from Aladdin Industrial Co., Ltd (Shanghai, China). All other chemicals and solvents were also furnished by Aladdin, and were of the highest commercial grade and used without further purification.

Preparation of inclusion complex

A 6.16616 g of HP-β-CD powder was dissolved in 22 mL of distilled water, resulting in a concentration of 4 mmol/L HP-β-CD. Subsequently, 0.38836 g of FA was dissolved in 6.2 mL of ethanol, also resulting in a concentration of 2 mmol/L. FA solution was then slowly added to the HP-β-CD solution with continuous stirring for 24 h at room temperature. The final clear and transparent solution was lyophilized at – 80 °C in a freeze dryer. After that, FA/HP-β-CD inclusion complex was produced in a 0.5:1 (mol/L) ratio.

A total of 9.0806 g of β-CD powder was dissolved in 250 mL of distilled water, resulting in a concentration of 8 mmol/L β-CD. The solution was stirred until achieving clarity, followed by the dissolution of 0.7774 g of FA in 24 mL of 70% ethanol to achieve a concentration of 4 mmol/L. The FA solution was then slowly added to the β-CD solution while continuously stirring for a duration of 24 h at room temperature. The subsequent steps were identical to the preparation process of the FA/HP-β-CD inclusion compound mentioned earlier. Ultimately, an FA/β-CD inclusion complex was formed in a 0.5:1 (mol/L) ratio.

Preparation of physical mixture

To prepare the physical mixture, which had the same molar ratio as the FA/HP-β-CD and FA/β-CD complex, FA and HP-β-CD or β-CD were mixed together using a mortar and ground uniformly for 5 min.

Fourier transform infrared spectroscopy (FT-IR)

The functional groups of FA, HP-β-CD, β-CD, FA and HP-β-CD physical mixture, FA and β-CD physical mixture, and the inclusion complex of FA/HP-β-CD and FA/β-CD were characterized by a BRUKER TENSORII spectrometer (PerkinElmer, USA). Measurements were obtained at the region of 4000 and 600 cm^{-1} with a resolution of 2 cm^{-1}.

X-ray diffractometry (XRD)

The XRD patterns of HP-β-CD, β-CD, FA, and the inclusion complex of FA/HP-β-CD and FA/β-CD were determined by X-ray diffractometer (Bruker D8 Advance,

Germany) with Ni-filtered Cu Kα radiation (45 kV, 35 mA). The XRD scans were conducted within a diffraction angle range of 10° to 45°.

Preparation of ODFs

Our previous studies have optimized the formulation of ODFs containing cyclodextrin inclusion complexes as follows: A 0.25 g of HPMC E5 and 0.05 g of low substituted hydroxypropyl cellulose (L-HPC) were dissolved in 10 mL of distilled water through stirring. Subsequently, inclusion compounds of 0.10 g of FA/β-CD (0.5:1) or FA/HP-β-CD (0.5:1) were added. The resulting mixture solutions were left at room temperature for 24 h to eliminate air bubbles. They were then poured into a petri dish and dried in a vacuum drying oven at 50 °C for 4 h. The resulting films were cut into rectangles measuring 2 × 3 cm, which were intended for one-time use. These rectangles were sealed and stored in an aluminum pack until further analysis.

Evaluation of ODFs

General properties

The moisture content of the ODF (2 × 3 cm) was determined by calculating the weight difference before and after drying in a drying oven for 48 h. The pH of the ODF surface was measured using a pH meter (Mettler Toledo FE28, Mettler Toledo AG, Zurich, Switzerland). Manual calipers were used to measure at least five pieces of ODF from five different points. The results were reported as the arithmetic mean and standard deviation.

Content in a film and content uniformity

At least five pieces of ODF (2 × 3 cm) were selected and dissolved in 100 mL of artificial salivary fluid (pH 6.8). The FA content in each ODF was quantified using UV spectrophotometry(Özakar et al. 2023). The standard curve for FA was established as: Y = 0.0701X − 0.0013, with an R^2 value of 0.9995. The FA content in each film was determined based on the standard curve. The content uniformity of the film was assessed following the methodology described by Sjholm et al. (2020).

Mechanical properties

The tensile strength was assessed utilizing a texture analyzer, specifically the TA new plus model from Stable Micro System Ltd. in London, UK. The experimental parameters were configured as follows: pre-test speed of 1 mm/s, test speed of 1 mm/s, trigger force of 5 g, stretched distance of 10 mm, and stretching speed of 1 mm/s. The film's two ends were affixed to the tensile probe, and the texture meter was vertically stretched at a consistent rate until the film ruptured, with the force exerted at that moment being recorded.

The folding endurance was determined following the method outlined by Vidyadhara et al. (2015). It was assessed through repetitive folding of a small strip at a consistent position until the film reached its breaking point. The total number of folds required for the film to break was recorded.

Disintegration time

The film, measuring 2 × 3 cm, was affixed to a test tube rack, with a petri dish positioned below. Two hundred microliters of an oral simulation solution, consisting of 1.3 g α-amylase dissolved in 1 mM $CaCl_2$ with a pH of 7.0, was then applied to the surface of the ODF. The disintegration time of the ODF was measured when the droplets successfully permeated the film.

In vitro release of FA from ODFs

In vitro release testing was conducted using three different dissolution media: simulated saliva fluid (pH = 7.0, containing 1.3 g of α-amylase dissolved in 1000 mL of 1 mmol/L $CaCl_2$ solution), simulated gastric fluid (pH = 2, containing 40.0 g of pepsin dissolved in 1000 mL of 0.01 mol/L HCl solution), and simulated intestinal fluid (pH = 7.0, containing 1.0 g of pancreatic enzymes and 10.0 g of bile salts dissolved in 1000 mL of 0.1 mol/L carbonate buffer). The release testing was conducted by referencing the work of Li et al. 2022). Oral samples were withdrawn at specific time intervals (10, 20, 30, 45, 60, 90, 120, 300, 600, 900 s), while gastric and intestinal samples were collected at different time points (5, 10, 15, 30, 45, 60, 90, 120, 150, 180 min). Then, the same volume of fresh medium at the same temperature was replenished. The absorbance at 313 nm was measured using UV spectrophotometry to determine the concentration of FA. The percentage of cumulative release was subsequently calculated as follows: Cumulative release =

$$P = Q_n/Q_0 \times 100\% \quad (1)$$

Where Q_n is cumulative release of FA of each digested sampling (mg), Q_0 is initial amount of FA (mg).

Release kinetics of FA from ODFs

Four conventional release models (Li et al. 2022), namely zero order, first order, Higuchi, and Ritger-Peppas, were employed to assess the kinetic model and mechanism of the release of FA. The equations used were as follows:

Zero order: $$M_t/M_\infty = k_0 t \quad (2)$$

First order: $$M_t/M_\infty = 1 - e^{-k_1 t} \quad (3)$$

Higuchi: $$M_t/M_\infty = k_h t^{1/2} \quad (4)$$

Ritger-peppas: $$M_t/M_\infty = k_{rp} t^n \quad (5)$$

Where M_t represents the cumulative release amount at time t, M_∞ represents the cumulative release amount at

infinite time. The constants k_0, k_1, k_h, and k_{rp} are associated with each kinetic model, while n is an index that relies on the release process.

Data processing and statistics analysis

All data were determined at least three times, and were presented as mean ± standard deviation, and one-way analysis of variance (ANOVA) was utilized for the statistical analysis (SPSS Inc., Chicago, USA). Tukey's multiple range tests were conducted at a significance level of 5% to determine significant differences. A p-value of ≤ 0.05 was considered indicative of such differences.

Results and discussion

FT-IR analysis

FT-IR spectroscopy can yield valuable insights into the interaction between CD and guest molecules. Fig. 1 illustrated the FT-IR spectra of various compounds, including HP-β-CD, β-CD, FA, the physical mixture of FA and HP-β-CD, as well as the inclusion complexes of FA/HP-β-CD (0.5:1) and FA/β-CD (0.5:1). The FT-IR spectrum clearly exhibits the absorption bands of FA, such as the –OH stretching at 3435 cm^{-1} and the aromatic nucleus in the range of 1620 to 1205 cm^{-1}. Additionally, the absorption peak at 1466 cm^{-1} was mainly caused by C–H deformations and aromatic ring vibrations. The peaks observed at 1691 and 1664 cm^{-1} were attributed to the C=O stretching vibration(Yang et al. 2018). The sharpness observed at 852 and 804 cm^{-1} was attributed to the presence of two adjacent hydrogen atoms on the phenyl ring (Shi et al. 2016). The peak observed at 1277 cm^{-1} was associated with the asymmetric stretching vibration of the C–O–C bond. The absorption observed at 1177 cm^{-1} was indicative of the characteristic peak of the carbonyl group (Shi et al. 2016).

In the case of HP-β-CD, the peaks observed at 2921 and 1190 cm^{-1} corresponded to the vibrations associated with C–H stretching (Janicke et al. 2011) and vibrations of the antisymmetric C–O–C glycosidic bridge stretching (Yu et al. 2021), respectively. The observed peaks at 1151 and 1024 cm^{-1} can be attributed to C–O stretching vibration (Sohn et al. 2003). Additionally, peaks were observed at 1642 cm^{-1} (indicating –OH stretching vibrations) and 1366 cm^{-1} (indicating $-CH_3$ bending).

The absence of new absorption peaks in the spectrum of the physical mixture of HP-β-CD and FA suggested that the mixture was merely a physical combination without any chemical reaction. In contrast, the FT-IR spectra of the FA/HP-β-CD inclusion complex closely resemble those of HP-β-CD, as evidenced by the significant reduction in characteristic peaks of FA at 3435, 1691, 1664, 1620 ~ 1205, 852 and 804 cm^{-1}. These spectral changes observed in this study provide evidence of the successful incorporation of FA within the cavity of HP-β-CD. Similar findings were reported by Wang et al. (2011).

Similarly, in relation to β-CD, the stretching vibration peak of C–H was observed at 1154 cm^{-1}, while the stretching vibration peak of C–O appeared at 1077 cm^{-1}. The resulting spectrum of the mixture can be described as a straightforward combination of the individual spectra of FA and β-CD.

In the inclusion complex of FA/β-CD (0.5:1), the peak intensity at 1024 cm^{-1} exhibited greater strength, whereas the peak intensities at 804, 852, 1620, and 1691 cm^{-1} were comparatively weaker. Additionally, the peak of FA at 3435 cm^{-1} experienced a shift to 3297 cm^{-1}, accompanied by an increase in the intensity of the broad peak. These observed variations in intensity and position of FA peaks suggested the formation of a novel substance between FA and β-CD.

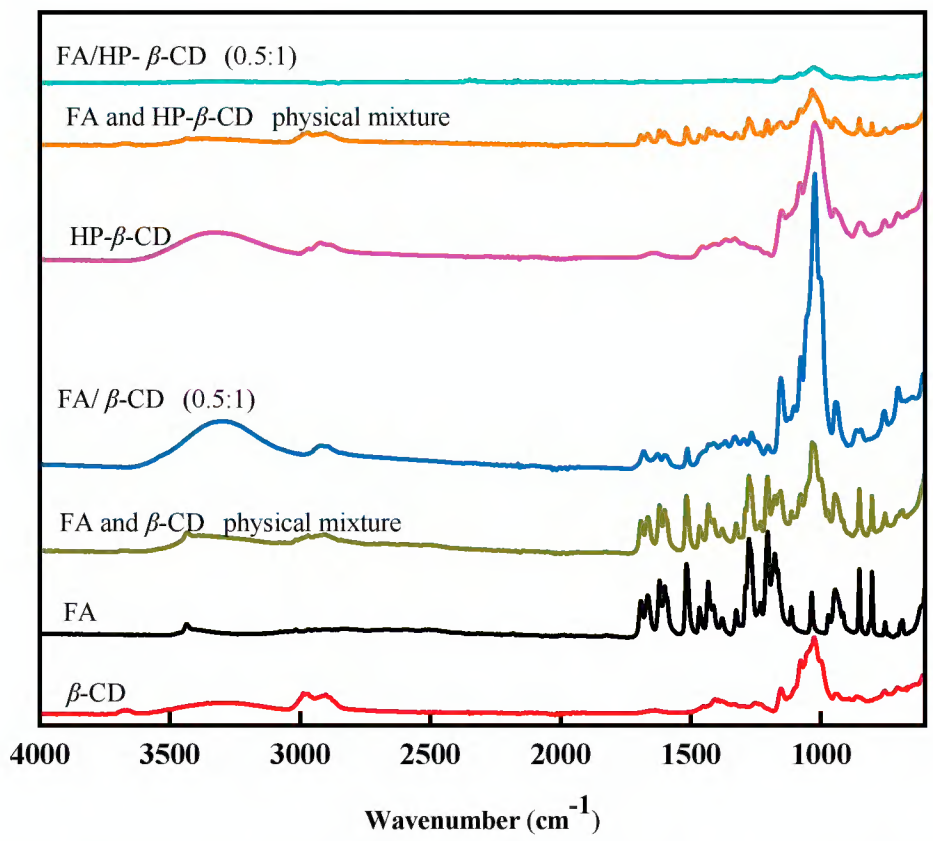

Figure 1. FT-IR of HP-β-CD, FA, FA and HP-β-CD physical mixture, β-CD, FA and β-CD physical mixture, FA/HP-β-CD (0.5:1) and FA/β-CD (0.5:1) inclusion complex.

XRD analysis

The XRD properties of the crystal lattice provide an effective means for elucidating the structure of the compound. The crystallinity of inclusion complex formation between guest and CD molecules can be achieved through the examination of various diffraction peaks in the x-ray diffraction pattern (Mura 2015). As depicted in Fig. 2, HP-β-CD exhibited a broad peak at 18.3°, indicating its amorphous nature. Conversely, FA displayed prominent and well-defined peaks at 10.4°, 12.8°, 15.6°, 17.4°, 26.5°, and 29.4°, along with minor peaks at 11.5°, 14.1°, 21.1°, 21.6°, 22.4°, 23.1°, 23.8, 24.6°, 36.1°, 39.1°, which confirmed its crystalline nature. These findings aligned with the previous research conducted by Wang et al. (2011). The diffraction pattern of the inclusion complex of FA/HP-β-CD closely resembled that of HP-β-CD, indicating a similarity in their structural characteristics. Additionally, the absence of FA's characteristic peak suggested a lack of crystallinity, which further supported the formation of the complex.

The diffraction spectrum of β-CD exhibited numerous distinct and intense diffraction peaks, indicating a clear crystalline structure. However, in the spectra of the FA/β-CD (0.5:1) inclusion complex, several sharp crystal diffraction peaks were no longer present, and instead, broad absorption peaks were observed at approximately 2θ values of 11.5°, 11.9°, 15.2°, and 17.6°. A reduction or elimination of the crystallinity of β-CD demonstrated a noteworthy chemical interaction between FA and β-CD within the inclusion compound. A comparable observation was made by Shao et al. (2014) in the study of inclusion complexes involving chlorogenic acid and cyclodextrin.

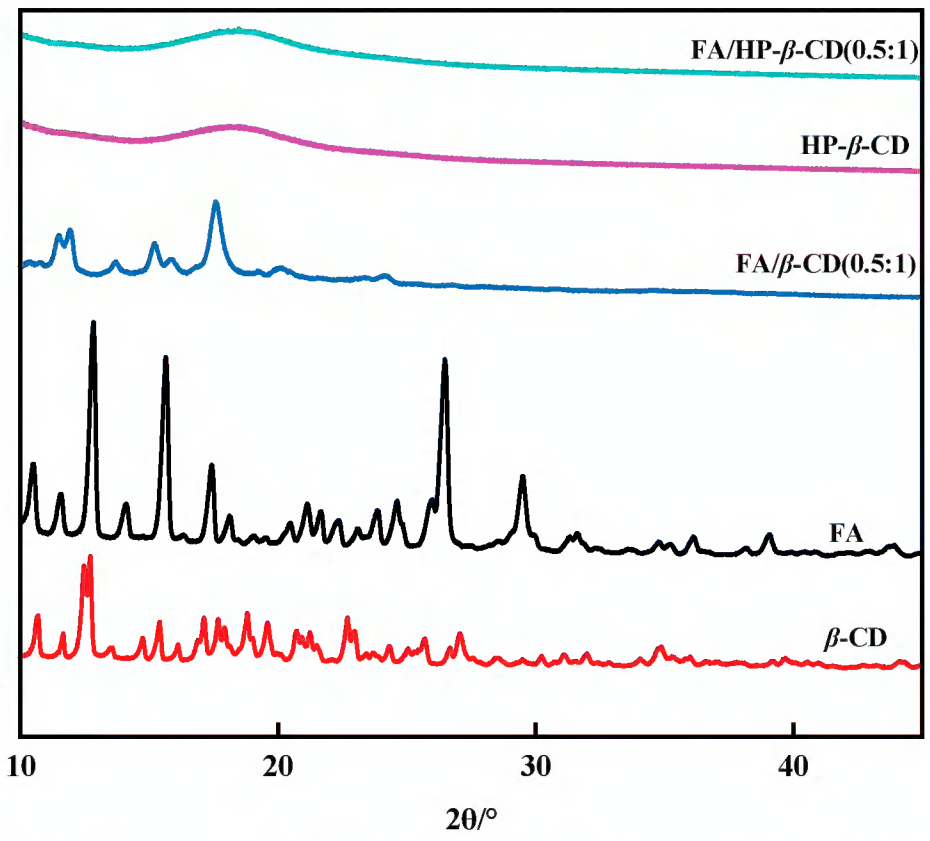

Figure 2. XRD patterns of HP-β-CD, FA, β-CD, FA/HP-β-CD (0.5:1) and FA/β-CD (0.5:1) inclusion complex.

General properties of the ODF

The importance of thickness lies in its direct relationship with the quantity of FA present in the ODF. The thickness of the ODF can be altered through variations in the base material, solute concentration, or additives. According to the study of Sha et al. (2022a), the film's thickness exhibited a positive correlation with the amount of forming materials incorporated. However, it is crucial to maintain an appropriate thickness that ensures comfortable application to the mucosa without causing discomfort, while also allowing sufficient handling and manipulation. The thickness of the film containing FA/β-CD (0.5:1) and FA/HP-β-CD (0.5:1) was presented in Table 1. Both formulations exhibited a comparable thickness of 0.06 mm, with no statistically significant difference observed ($p < 0.05$). Nair et al. (2013) proposed that the optimal thickness for ODFs ranged from 0.05 to 1.00 mm. Notably, the thicknesses of the films prepared in this study fell within the recommended range for ODFs.

The moisture content of the ODF was shown in Table 1, which is known to impact the film's quality properties. A film possessing a diminished moisture content may exhibit increased fragility, whereas an excessive moisture content may give rise to adhesive films that have the potential to adhere to the patient's fingers and/or packaging material, thereby augmenting the likelihood of microbial proliferation (Lir et al. 2007; Borges et al. 2015). Presently, there are no established pharmacopeia standards for the moisture content of ODFs (Visser et al. 2015). In the existing body of literature, the moisture content of investigated films has typically been below 10%(Foo et al. 2018; Sha et al. 2022a). Nair et al. (2018) have advocated for a moisture content of less than 5% in buccal films. The water content of the films prepared in this study, which contained FA/β-CD (0.5:1) and FA/HP-β-CD (0.5:1), were determined to be 6.20% and 4.66%, respectively. These findings suggest that the ODF with FA/HP-β-CD (0.5:1) falls within the recommended range as stated by Nair et al. (2018).

The FA content of the ODF prepared with FA/HP-β-CD (0.5:1) inclusion compound was measured to be 8.95 mg/film (Table 1), which was higher than the film prepared with FA/β-CD (0.5:1) inclusion compound (4.46 mg/film). These results indicated that the film incorporating FA/HP-β-CD (0.5:1) inclusion complex can effectively provide nutritional supplementation with fewer pieces compared to the film incorporating FA/β-CD (0.5:1) inclusion complex. It also indicated that the film containing FA/HP-β-CD (0.5:1) inclusion complex offered greater convenience for users. Furthermore, the content uniformity of the two films was measured at 1.32% and 0.46%, respectively, both of which fall within the acceptable range of less than 15% (Shang et al. 2018).

The ODF should have the ability to dissolve or disperse upon contact with saliva when placed on the tip of the tongue, in accordance with the intraoral pH. It is preferable for the surface pH of the ODF to closely resemble that of physiological saliva (ranging from 5.8 to 7.4) in order to ensure a comfortable mouthfeel. If the pH of an ODF falls outside this range, it may lead to local mucosal irritation and discomfort upon administration (Woertz et al. 2013). In this study, both film formulations had a pH of 6.7 (Table 1), which fell within the range of physiological saliva. The films prepared in this study exhibited no irritation to the oral cavity and met the pH requirements of the ODF.

Table 1. Physico-chemical properties of ODFs containing FA/β-CD (0.5:1) and FA/HP-β-CD (0.5:1).

Films	Thickness (mm)	Moisture content (%)	Content (mg/film)	Content uniformity (%)	Surface pH
FA/β-CD (0.5:1)	0.06 ± 0.005 a	6.20 ± 0.42 a	4.46 ± 0.15 b	1.32 a	6.7 ± 0.01 a
FA/HP-β-CD (0.5:1)	0.06 ± 0.003 a	4.66 ± 0.38 b	8.95 ± 0.29 a	0.46 b	6.7 ± 0.02 a

Note: Different lowercase letters in the table indicated significant differences in each column at the $P < 0.05$ level.

Mechanical properties and disintegration time of ODFs

It was reported that the mechanical properties of ODF mainly depend on the integrity of the network structure in the film matrix. Tensile strength is a crucial mechanical parameter that illustrates a film's flexibility and strength(-Siripruekpong et al. 2023). Additionally, it had been observed that the tensile strength of the film was inversely related to its thickness (Salawi and Nazzal 2018). According to Table 2, the tensile strength of the film containing FA/β-CD (0.5:1) and FA/HP-β-CD (0.5:1) was measured to be 17.99 and 15.94 MPa, respectively, suggesting that the tensile strength of the film containing FA/β-CD (0.5:1) was significantly higher than that of the film with FA/HP-β-CD (0.5:1) ($p < 0.05$). The observed disparity in film characteristics between FA/β-CD (0.5:1) and FA/HP-β-CD (0.5:1) may be attributed to the former exhibiting a more compact and regular network structure. These findings closely resemble those obtained from films incorporating catechin/β-cyclodextrin inclusions (Sha et al. 2022b).

Table 2. Mechanical properties and disintegration time of ODF.

Films	Tensile strength (MPa)	Folding endurance (times)	Disintegration time (s)
FA/β-CD (0.5:1)	17.99 ± 0.70 a	54 ± 1 a	29.44 ± 0.72 a
FA/HP-β-CD (0.5:1)	15.94 ± 0.28 b	55 ± 1 a	29.14 ± 0.50 a

Note: Different lowercase letters in the table indicated significant differences in each column at the $P < 0.05$ level.

Folding endurance is an extremely important parameter in terms of the stability of films. The attainment of an optimal folding endurance for the film is crucial in ensuring the preservation of the ODF's integrity throughout its production, handling, and transportation processes. Furthermore, it was reported that the folding endurance increased proportionally with the augmentation of both polymer and plasticizer quantities (Ashraf et al. 2023). The folding endurance of film containing FA/β-CD (0.5:1) and FA/HP-β-CD (0.5:1) was found to be approximately 55 times (Table 2), which fell below the recommended threshold of 300 times or more (Yir-Erong et al. 2019). Consequently, our future research will be primarily focused on enhancing the folding endurance of the ODF while simultaneously considering safety and economic advantages.

The ODF can be graded according to the different disintegration time. It has been proved that the disintegration time of the film was influenced by both the thickness and network structure within the film matrix. The enhanced network structure and increased film thickness contributed to the heightened resistance against droplet penetration, leading to an extended disintegration time (Sha et al. 2022a). ODFs with thicknesses ranging from 0.05 to 0.15 mm exhibited rapid dissolution in the oral cavity (Chaturvedi et al. 2011). The European Pharmacopoeia specifies a disintegration time of up to 3 minutes for orally disintegrating tablets (ODTs), while the FDA and USP guidelines recommend a disintegration time of 30 seconds or less (Özakar et al. 2023). The films prepared in this study, as indicated in Table 2, demonstrated a disintegration time of less than 30 s, which met the requirements of ODF on disintegration time.

Release behaviors of FA from ODFs

Release behaviors of FA in stimulated oral fluid

As depicted in Fig. 3A, the ODF composed of FA/β-CD (0.5:1) inclusion compound exhibited a cumulative release rate of 45.07% within a duration of 900 s. In contrast, the ODF comprising FA/HP-β-CD (0.5:1) inclusion compound demonstrated a release rate of 85.91% at 10 s. These elevated release rates may facilitate swift absorption by the oral mucosa. Furthermore, when comparing the two ODFs, it was observed that the ODF composed of FA/HP-β-CD (0.5:1) inclusion compound exhibited a more pronounced release effect in the oral cavity, suggesting its suitability for ODF preparation.

Release behaviors of FA in stimulated gastric fluid

As presented in Fig. 3B, the ODF composed of FA/β-CD (0.5:1) inclusion compound exhibited a cumulative release rate of 43.29% within 180 min, which closely resembled the cumulative release observed in the simulated oral environment. The cumulative release rate of the ODF composed of FA/HP-β-CD (0.5:1) inclusion compound reached 57.56% within a duration of 180 min, which was found to be lower compared to its corresponding cumulative release in the simulated oral environment. In addition, the release effect of FA/HP-β-CD (0.5:1) in the gastric simulated solution was superior to that of FA/β-CD (0.5:1).

Release behaviors of FA in stimulated intestinal fluid

As can be seen from Fig. 3C, The ODF composed of FA/β-CD (0.5:1) inclusion compound exhibited a cumulative release rate of 65.43% within 180 min. Similarly, the cumulative release of FA/HP-β-CD (0.5:1) film during the same duration reached 97.82%. These findings indicated that the release of FA in the ODFs containing FA/HP-β-CD (0.5:1) outperformed its counterparts in simulated intestinal fluid.

In conclusion, the cumulative release rate of the two ODFs across three distinct simulated digestive environments followed the order of intestine > oral cavity > stomach. Furthermore, within the same simulated environment, the cumulative release of FA from FA/HP-β-CD (0.5:1) was greater than that from FA/β-CD (0.5:1) under *in-vitro* simulated digestive conditions, indicating the superiority of the film made from FA/HP-β-CD (0.5:1) over that of FA/β-CD (0.5:1). This may be due to the fact that HP-β-CD exhibited higher solubility compared to β-CD. This finding aligned with the study reported by Panraksa et al. (2020), who demonstrated that the utilization of more hydrophilic polymers and the amorphous state of the drug facilitated the rapid release of the drug. The incorporation

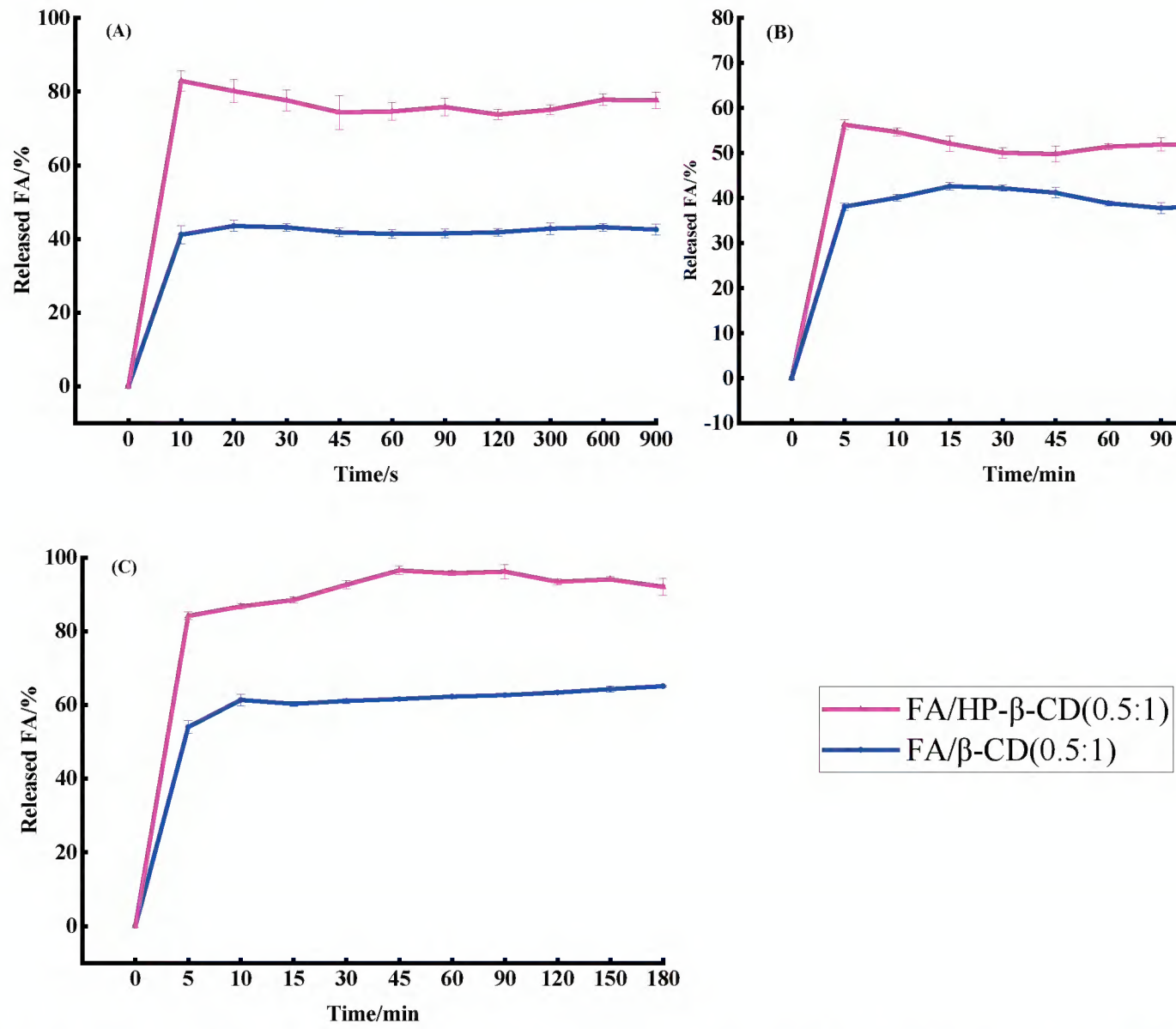

Figure 3. Release curve of FA from ODFs in simulated oral (**A**), gastric (**B**), and intestinal (**C**) fluid.

of FA resulted in an improvement in hydrophilicity and obscured the crystal structure of FA, potentially explaining the higher cumulative release rate observed in the FA/HP-β-CD film compared to the FA/β-CD film throughout the *in-vitro* digestion process.

Determination of release kinetics in vitro

The capacity to predict the release kinetics of active substances is a critical characteristic of delivery systems, as it significantly affects their safety and efficacy by influencing absorption, the speed of reaching the target site, and the quantity of active substances. The findings of the FA release kinetic model were presented in Table 3. The determination of the model's order can be further evaluated by considering the model with the highest coefficient (R^2) as superior.

As shown in Table 3, it was observed that in the oral simulation condition, the first-order kinetic model ($R^2 = 0.9854$) was the most appropriate for the ODF containing FA/HP-β-CD (0.5:1). However, the R^2 value for ODF containing FA/β-CD (0.5:1) were relatively low, with the highest R^2 value of 0.1943 observed for the first-order kinetic model. In the simulated gastric environment, the most suitable model for ODFs containing FA/HP-β-CD (0.5:1) and FA/β-CD (0.5:1) was found to be the first-order kinetic model, exhibiting a highest R^2 values of 0.9842 and 0.9771, respectively. In the context of the intestinal simulation environment, the release of FA from ODFs composed of FA/HP-β-CD (0.5:1) and FA/β-CD (0.5:1) inclusion compounds were found to adhere to a first-order kinetic model. This was evidenced by the R^2 values of 0.9899 and 0.9950, respectively.

In summary, with the exception of the ODF containing FA/β-CD (0.5:1) inclusion compound in the oral simulation environment, the release of FA from the ODFs containing FA/β-CD (0.5:1) and FA/HP-β-CD (0.5:1) inclusion compounds in three simulated digestive environments can be well described by the first-order kinetic model. This

Table 3. Linear regression results of FA release pattern from the films *in-vitro* simulated digestive environment.

Kinetic model	ODFs	Oral		Gastric		Intestinal	
		Linear regression	R^2	Linear regression	R^2	Linear regression	R^2
Zero Order	FA/HP-β-CD(0.5:1)	$y = 77.25x - 0.0026$	0.0716	$y = 53.07x - 0.0163$	0.2340	$y = 89.63x - 0.0336$	0.2472
	FA/β-CD(0.5:1)	$y = 42.11x + 0.001$	0.0997	$y = 40.89x - 0.0209$	0.4291	$y = 58.96x - 0.0378$	0.5842
First Order	FA/HP-β-CD(0.5:1)	$y = 76.68(1 - e^{-3.38x})$	0.9854	$y = 51.92(1 - e^{-555.45x})$	0.9842	$y = 93.16(1 - e^{-0.44x})$	0.9899
	FA/β-CD(0.5:1)	$y = 42.43(1 - e^{-0.36x})$	0.1943	$y = 39.57(1 - e^{-0.67x})$	0.9771	$y = 62.64(1 - e^{-0.39x})$	0.9950
Higuchi	FA/HP-β-CD(0.5:1)	$y = 0.1255x^{1/2} + 78.18$	0.1480	$y = -0.3188x^{1/2} + 54.32$	0.3567	$y = 0.6977x^{1/2} + 86.76$	0.4200
	FA/β-CD(0.5:1)	$y = 0.0293x^{1/2} + 41.96$	0.0944	$y = -0.3030x^{1/2} + 41.70$	0.3608	$y = 0.6434x^{1/2} + 56.77$	0.6778
Ritger-peppas	FA/HP-β-CD(0.5:1)	$y = 80.43(x^{-0.01})$	0.0889	$y = 56.46(x^{-0.02})$	0.5128	$y = 81.46(x^{0.03})$	0.7247
	FA/β-CD(0.5:1)	$y = 41.85(x^{-0.003})$	0.0291	$y = 42.72(x^{-0.02})$	0.3215	$y = 54.25(x^{0.03})$	0.9003

finding was in agreement with Özakar et al.'s observation that the initial dissolution stage of a poorly water-soluble drug incorporated within a water-soluble matrix can be accurately described by the first-order kinetic model (Özakar et al. 2023), thus supporting our own conclusions. However, Li et al. (2022) provided evidence that FA/β-CD (0.5:1) inclusion complexes conformed to the Ritger-Peppas model when tested in distilled water, which contrasted with our own findings. This discrepancy may be attributed to variations in the composition of the released solution. Additionally, it has been noted that alterations in the film preparation method can lead to changes in the release mechanisms(Zhang et al. 2021).

Conclusions

HPMC-based ODFs were successfully produced, incorporating FA/β-CD (0.5:1) and FA/HP-β-CD (0.5:1) complexes. The resulting ODFs exhibited rapid disintegration times (< 30 s) when tested *in vitro*. Additionally, these ODFs possessed low moisture content and thinner thickness, both falling well below the recommended thresholds. *In vitro* dissolution testing revealed that both ODF formulations conformed closely to the first-order kinetic model. Notably, ODFs composed of FA/HP-β-CD in a 0.5:1 ratio exhibited a higher cumulative release rate of FA in an *in vitro* simulated digestive environment compared to ODFs containing FA/β-CD in the same ratio. This finding suggests that the FA/HP-β-CD (0.5:1) formulation may be more suitable for the development of ODFs. The study underscores the potential of employing ODFs in combination with CDs as a promising delivery system for natural active compounds.

Author contributions

Junli Lv: experimental design; analysis; writing original draft. Jiali Zou: project administration. Jianjiao Niu: data analysis. Guoze Wang: supervision, review & editing.

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